Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention

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Abstract

Introduction Melatonin has been studied in headache disorders. Amitriptyline is efficacious for migraine prevention, but its unfavourable side effect profile limits its use.

Methods A randomised, double-blind, placebo-controlled study was carried out. Men and women, aged 18–65 years, with migraine with or without aura, experiencing 2–8 attacks per month, were enrolled. After a 4-week baseline phase, 196 participants were randomised to placebo, amitriptyline 25 mg or melatonin 3 mg, and 178 took a study medication and were followed for 3 months (12 weeks). The primary outcome was the number of migraine headache days per month at baseline versus last month. Secondary end points were responder rate, migraine intensity, duration and analgesic use. Tolerability was also compared between groups.

Results Mean headache frequency reduction was 2.7 migraine headache days in the melatonin group, 2.2 for amitriptyline and 1.1 for placebo. Melatonin significantly reduced headache frequency compared with placebo (p=0.009), but not to amitriptyline (p=0.19). Melatonin was superior to amitriptyline in the percentage of patients with a greater than 50% reduction in migraine frequency. Melatonin was better tolerated than amitriptyline. Weight loss was found in the melatonin group, a slight weight gain in placebo and significantly for amitriptyline users.

Conclusions Melatonin 3 mg is better than placebo for migraine prevention, more tolerable than amitriptyline and as effective as amitriptyline 25 mg.

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Use of Plant-Based Therapies and Menopausal Symptoms - A Systematic Review and Meta-analysis

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Abstract

Importance  Between 40% and 50% of women in Western countries use complementary therapies to manage menopausal symptoms.

Objective  To determine the association of plant-based therapies with menopausal symptoms, including hot flashes, night sweats, and vaginal dryness.

Data Sources  The electronic databases Ovid MEDLINE, EMBASE, and Cochrane Central were systematically searched to identify eligible studies published before March 27, 2016. Reference lists of the included studies were searched for further identification of relevant studies.

Study Selection  Randomized clinical trials that assessed plant-based therapies and the presence of hot flashes, night sweats, and vaginal dryness.

Data Extraction  Data were extracted by 2 independent reviewers using a predesigned data collection form.

Main Outcomes and Measures  Hot flashes, night sweats, and vaginal dryness.

Results  In total, 62 studies were identified, including 6653 individual women. Use of phytoestrogens was associated with a decrease in the number of daily hot flashes (pooled mean difference of changes, −1.31 [95% CI, −2.02 to −0.61]) and vaginal dryness score (pooled mean difference of changes, −0.31 [95% CI, −0.52 to −0.10]) between the treatment groups but not in the number of night sweats (pooled mean difference of changes, −2.14 [95% CI, −5.57 to 1.29]). Individual phytoestrogen interventions such as dietary and supplemental soy isoflavones were associated with improvement in daily hot flashes (pooled mean difference of changes, −0.79 [−1.35 to −0.23]) and vaginal dryness score (pooled mean difference of changes, −0.26 [−0.48 to −0.04]). Several herbal remedies, but not Chinese medicinal herbs, were associated with an overall decrease in the frequency of vasmotor symptoms. There was substantial
heterogeneity in quality across the available studies, and 46 (74%) of the included randomized clinical trials demonstrated a high risk of bias within 3 or more areas of study quality.

**Conclusions and Relevance** This meta-analysis of clinical trials suggests that composite and specific phytoestrogen supplementations were associated with modest reductions in the frequency of hot flashes and vaginal dryness but no significant reduction in night sweats. However, because of general suboptimal quality and the heterogeneous nature of the current evidence, further rigorous studies are needed to determine the association of plant-based and natural therapies with menopausal health.
Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number

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Elevated basal serum tryptase levels are present in 4–6% of the general population, but the cause and relevance of such increases are unknown1,2. Previously, we described subjects with dominantly inherited elevated basal serum tryptase levels associated with multisystem complaints including cutaneous flushing and pruritus, dysautonomia, functional gastrointestinal symptoms, chronic pain, and connective tissue abnormalities, including joint hypermobility. Here we report the identification of germline duplications and triplications in the TPSAB1 gene encoding α-tryptase that segregate with inherited increases in basal serum tryptase levels in 35 families presenting with associated multisystem complaints. Individuals harboring alleles encoding three copies of α-tryptase had higher basal serum levels of tryptase and were more symptomatic than those with alleles encoding two copies, suggesting a gene-dose effect. Further, we found in two additional cohorts (172 individuals) that elevated basal serum tryptase levels were exclusively associated with duplication of α-tryptase–encoding sequence in TPSAB1, and affected individuals reported symptom complexes seen in our initial familial
cohort. Thus, our findings link duplications in TPSAB1 with irritable bowel syndrome, cutaneous complaints, connective tissue abnormalities, and dysautonomia.

**Mortality In Patients With Myalgic Encephalomyelitis And Chronic Fatigue Syndrome.**

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Abstract Background: There is a dearth of research examining mortality in individuals with myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS). Some studies suggest there is an elevated risk of suicide and earlier mortality compared to national norms. However, findings are inconsistent as other researchers have not found significant increases in all-cause mortality for patients.

Objective: This study sought to determine if patients with ME or CFS are reportedly dying earlier than the overall population from the same cause.

Methods: Family, friends, and caregivers of deceased individuals with ME or CFS were recruited through social media, patient newsletters, emails, and advocate websites. This study analyzed data including cause and age of death for 56 individuals that had ME or CFS.

Results: The findings suggest patients in this sample are at a significantly increased risk of earlier all-cause (M = 55.9 years) and cardiovascular-related (M = 58.8 years) mortality, and they had a directionally lower mean age of death for suicide (M = 41.3 years) and cancer (M = 66.3 years) compared to the overall U.S. population [M = 73.5 (all-cause), 77.7 (cardiovascular), 47.4 (suicide), and 71.1 (cancer) years of age].

Conclusions: The results suggest there is an increase in risk for earlier mortality in patients with ME and CFS. Due to the small sample size, the findings should be replicated to determine if the directional differences for suicide and cancer mortality are significantly different from the overall U.S. population.

Source: http://bit.ly/2dYeqi1
Randomized, Double-blind, Placebo-controlled Phase III Trial of Duloxetine Monotherapy in Japanese Patients With Chronic Low Back Pain

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Disclosures

Abstract

Study Design. A 14-week, randomized, double-blind, multicenter, placebo-controlled study of Japanese patients with chronic low back pain (CLBP) who were randomized to either duloxetine 60 mg once daily or placebo.

Objective. This study aimed to assess the efficacy and safety of duloxetine monotherapy in Japanese patients with CLBP.

Summary of Background Data. In Japan, duloxetine is approved for the treatment of depression, diabetic neuropathic pain, and pain associated with fibromyalgia; however, no clinical study of duloxetine has been conducted for CLBP.

Methods. The primary efficacy measure was the change in the Brief Pain Inventory (BPI) average pain score from baseline to Week 14. Secondary efficacy measures included BPI pain (worst pain, least pain, pain right now), Patient's Global Impression of Improvement, Clinical Global Impressions of Severity, and Roland-Morris Disability Questionnaire, among other measures, and safety and tolerability.

Results. In total, 458 patients were randomized to receive either duloxetine (n = 232) or placebo (n = 226). The BPI average pain score improved significantly in the duloxetine group compared with that in the placebo group at Week 14 [-2.43 ± 0.11 vs. -1.96 ± 0.11, respectively; between-group difference (95% confidence interval), -0.46 [-0.77 to-0.16]; P = 0.0026]. The duloxetine group showed significant improvement in many secondary measures compared with the placebo group, including BPI pain (least pain, pain right now) (between-group difference: -1.69 ± 0.10, P = 0.0009; -2.42 ± 0.12, P = 0.0230, respectively), Patient's Global Impression of Improvement (2.46 ± 0.07, P = 0.0026), Clinical Global Impressions of Severity (-1.46 ± 0.06, P = 0.0019), and Roland-Morris Disability Questionnaire (-3.86 ± 0.22, P = 0.0439). Adverse events occurring at a significantly higher incidence in the duloxetine group were somnolence, constipation, nausea, dizziness, and dry mouth, most of which were mild or moderate in severity and were resolved or improved.

Conclusion. Duloxetine 60 mg was effective and well tolerated in Japanese CLBP patients.
Abstract

Objectives. RA-related fatigue is common and debilitating, but does not always respond to immunotherapy. In the context of anti-TNF therapy, we aimed to examine whether patients achieving disease remission experienced remission of fatigue.

Methods. Data from the British Society for Rheumatology Biologics Register for RA were used. In participants with severe baseline fatigue [36-item Short Form Health Survey (SF-36) vitality score \(\leq 12.5\)], we identified those in disease remission [28-joint DAS (DAS28) <2.6] by 6 months. Fatigue response was evaluated according to partial (SF-36 vitality score >12.5) and complete remission (SF-36 vitality score >50) at follow-up. Demographic (e.g. sex, age), clinical (e.g. inflammation, joint erosion and co-morbidities) and psychosocial (e.g. SF-36 domains and HAQ) characteristics were compared between responder and non-responder groups.

Results. Severe baseline fatigue was reported by 2652 participants, of whom 271 (10%) achieved a DAS28 <2.6 by 6 months. In total, 225 participants (83%) reported partial remission and were distinguished from those who did not by better health status on all psychosocial domains. Far fewer [n = 101 (37.3%)] reported full fatigue remission. In addition to reporting clinically poorer health status, they were distinguished on the basis of a history of hypertension, depression and stroke as well as baseline treatment use of steroids and antidepressants.

Conclusion. Despite achieving clinical remission, many RA patients do not achieve complete remission of their fatigue. Therefore, despite being important in overall disease control, reductions in disease
activity are not always sufficient to ameliorate fatigue, so other symptom-specific management approaches must be considered for those for whom fatigue does not resolve.

fatigue, disease activity, remission

Clinical Science
Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome

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Metabolism

Abstract

Myalgic encephalopathy/chronic fatigue syndrome (ME/CFS) is a debilitating disease of unknown etiology, with hallmark symptoms including postexertional malaise and poor recovery. Metabolic dysfunction is a plausible contributing factor. We hypothesized that changes in serum amino acids may disclose specific defects in energy metabolism in ME/CFS. Analysis in 200 ME/CFS patients and 102 healthy individuals showed a specific reduction of amino acids that fuel oxidative metabolism via the TCA cycle, mainly in female ME/CFS patients. Serum 3-methylhistidine, a marker of endogenous protein catabolism, was significantly increased in male patients. The amino acid pattern suggested functional impairment of pyruvate dehydrogenase (PDH), supported by increased mRNA expression of the inhibitory PDH kinases 1, 2, and 4; sirtuin 4; and PPARδ in peripheral blood mononuclear cells from both sexes. Myoblasts grown in presence of serum from patients with severe ME/CFS showed metabolic adaptations, including increased mitochondrial respiration and excessive lactate secretion. The amino acid changes could not be explained by symptom severity, disease duration, age, BMI, or physical activity level among patients. These findings are in agreement with the clinical disease presentation of ME/CFS, with inadequate ATP generation by oxidative phosphorylation and excessive lactate generation upon exertion.
Cytokine Inhibition in Patients With Chronic Fatigue Syndrome: A Randomized Trial

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Abstract

Background:
Interleukin-1 (IL-1), an important proinflammatory cytokine, is suspected to play a role in chronic fatigue syndrome (CFS).

Objective:
To evaluate the effect of subcutaneous anakinra versus placebo on fatigue severity in female patients with CFS.

Design:
Randomized, placebo-controlled trial from July 2014 to May 2016. Patients, providers, and researchers were blinded to treatment assignment. (ClinicalTrials.gov: NCT02108210)

Setting:
University hospital in the Netherlands.

Patients:
50 women aged 18 to 59 years with CFS and severe fatigue leading to functional impairment.

Intervention:
Participants were randomly assigned to daily subcutaneous anakinra, 100 mg (n = 25), or placebo (n = 25) for 4 weeks and were followed for an additional 20 weeks after treatment (n = 50).

Measurements:
The primary outcome was fatigue severity, measured by the Checklist Individual Strength subscale (CIS-fatigue) at 4 weeks. Secondary outcomes were level of impairment, physical and social functioning, psychological distress, and pain severity at 4 and 24 weeks.

Results:
At 4 weeks, 8% (2 of 25) of anakinra recipients and 20% (5 of 25) of placebo recipients reached a fatigue level within the range reported by healthy persons. There were no clinically important or statistically significant differences between groups in CIS-fatigue score at 4 weeks (mean difference, 1.5 points [95% CI, −4.1 to 7.2 points]) or the end of follow-up. No statistically significant between-group differences were seen for any secondary outcome at 4 weeks or the end of follow-up. One patient in the anakinra group discontinued treatment because of an adverse event. Patients in the anakinra group had more injection site reactions (68% [17 of 25] vs. 4% [1 of 25]).

Limitation:
Small sample size and wide variability in symptom duration; inclusion was not limited to patients with postinfectious symptoms.
Conclusion:

Peripheral IL-1 inhibition using anakinra for 4 weeks does not result in a clinically significant reduction in fatigue severity in women with CFS and severe fatigue.
Sex Differences in Microglia Activity within the Periaqueductal Gray of the Rat: A Potential Mechanism Driving the Dimorphic Effects of Morphine

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Abstract

Although morphine remains the primary drug prescribed for alleviation of severe or persistent pain, both preclinical and clinical studies have shown that females require 2-3 times more morphine than males to produce comparable levels of analgesia. In addition to binding to the neuronal μ opioid receptor (MOR), morphine binds to the innate immune receptor toll-like receptor 4 (TLR4) localized primarily on microglia. Morphine action at TLR4 initiates a neuroinflammatory response that directly opposes the analgesic effects of morphine. Here we test the hypothesis that the attenuated response to morphine observed in females is the result of increased microglia activation in the periaqueductal gray (PAG), a central locus mediating the antinociceptive effects of morphine. We report that while no overall sex differences in the density of microglia were noted within the PAG of male or female rats, microglia exhibited a more “activated” phenotype in females at baseline, with the degree of activation a significant predictor of morphine ED50 values. Priming microglia with LPS induced greater microglia activation in the PAG of females compared with males that was accompanied by increased transcription levels of IL-1ß and a significant rightward shift in the morphine dose response curve. Blockade of morphine binding to PAG TLR4 with (+)-naloxone significantly potentiated morphine antinociception in females such that no sex differences in ED50 were observed. These results demonstrate that PAG microglia are sexually dimorphic in both basal and LPS-induced activation, and contribute to the sexually dimorphic effects of morphine in the rat.

SIGNIFICANCE STATEMENT

We demonstrate that PAG microglia contribute to the sexually dimorphic effects of morphine. Specifically, we report that increased activation of microglia in the PAG contributes to the attenuated response to morphine observed in females. Our data further implicate the innate immune receptor TLR4 as an underlying mechanism mediating these effects, and establish that TLR4 inhibition in the PAG of females reverses the sex differences in morphine responsiveness. These data suggest novel methods to improve current opioid-based pain management via inhibition of glial TLR4, and illustrate the necessity for sex-specific research and individualized treatment strategies for the management of pain in men and women.

Footnotes

- The authors report no conflict of interest
- National Institutes of Health Grant DA16272 awarded to A.Z.M. supported this work. (-)-Morphine sulfate and (+)-naloxone were kindly provided by the National Institute on Drug Abuse drug supply program. The authors thank Lauren Hanus and Alyssa Bartlett for their technical assistance.
Abstract

Background

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a debilitating idiopathic disease characterized by unexplained fatigue that fails to resolve with sufficient rest. Diagnosis is based on a list of symptoms and exclusion of other fatigue-related health conditions. Despite a heterogeneous patient population, immune and hypothalamic-pituitary-adrenal (HPA) axis function differences, such as enhanced negative feedback to glucocorticoids, are recurring findings in ME/CFS studies. Epigenetic modifications, such as CpG methylation, are known to regulate long-term phenotypic differences and previous work by our group found DNA methylome differences in ME/CFS, however the relationship between DNA methylome modifications, clinical and functional characteristics associated with ME/CFS has not been examined.

Methods

We examined the DNA methylome in peripheral blood mononuclear cells (PBMCs) of a larger cohort of female ME/CFS patients using the Illumina HumanMethylation450 BeadChip Array. In parallel to the DNA methylome analysis, we investigated in vitro glucocorticoid sensitivity differences by stimulating PBMCs with phytohaemagglutinin and suppressed growth with dexamethasone. We explored DNA methylation differences using bisulfite pyrosequencing and statistical permutation. Linear regression was implemented to discover epigenomic regions associated with self-reported quality of life and network analysis of gene ontology terms to biologically contextualize results.

Results

We detected 12,608 differentially methylated sites between ME/CFS patients and healthy controls predominantly localized to cellular metabolism genes, some of which were also related to self-reported quality of life health scores. Among ME/CFS patients, glucocorticoid sensitivity was associated with differential methylation at 13 loci.

Conclusions
Our results indicate DNA methylation modifications in cellular metabolism in ME/CFS despite a heterogeneous patient population, implicating these processes in immune and HPA axis dysfunction in ME/CFS. Modifications to epigenetic loci associated with differences in glucocorticoid sensitivity may be important as biomarkers for future clinical testing. Overall, these findings align with recent ME/CFS work that point towards impairment in cellular energy production in this patient population.
Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine

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Share:

BACKGROUND
Which, medication, if any, to use to prevent the headache of pediatric migraine has not been established.

METHODS
We conducted a randomized, double-blind, placebo-controlled trial of amitriptyline (1 mg per kilogram of body weight per day), topiramate (2 mg per kilogram per day), and placebo in children and adolescents 8 to 17 years of age with migraine. Patients were randomly assigned in a 2:2:1 ratio to receive one of the medications or placebo. The primary outcome was a relative reduction of 50% or more in the number of headache days in the comparison of the 28-day baseline period with the last 28 days of a 24-week trial. Secondary outcomes were headache-related disability, headache days, number of trial completers, and serious adverse events that emerged during treatment.

RESULTS
A total of 361 patients underwent randomization, and 328 were included in the primary efficacy analysis (132 in the amitriptyline group, 130 in the topiramate group, and 66 in the placebo group). The trial was concluded early for futility after a planned interim analysis. There were no significant between-group differences in the primary outcome, which occurred in 52% of the patients in the amitriptyline group, 55% of those in the topiramate group, and 61% of those in the placebo group (amitriptyline vs. placebo, \(P=0.26\); topiramate vs. placebo, \(P=0.48\); amitriptyline vs. topiramate, \(P=0.49\)). There were also no significant between-group differences in headache-related disability, headache days, or the percentage of patients who completed the 24-week treatment period. Patients who received amitriptyline or topiramate had higher rates of several adverse events than those receiving placebo, including fatigue (30% vs. 14%) and dry mouth (25% vs. 12%) in the amitriptyline group and paresthesia (31% vs. 8%) and weight loss (8% vs. 0%) in the topiramate group. Three patients in the amitriptyline group had serious adverse events of altered mood, and one patient in the topiramate group had a suicide attempt.
CONCLUSIONS
There were no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline, topiramate, or placebo over a period of 24 weeks. The active drugs were associated with higher rates of adverse events. (Funded by the National Institutes of Health; CHAMP ClinicalTrials.gov number, NCT01581281).
Do low vitamin D levels increase the risk for myalgia in patients who are taking statins?

Response from Philip J. Gregory, PharmD
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About 1%-2% of patients who take hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins for hyperlipidemia develop muscle pain. This myalgia can feel like the aches and pains experienced with the flu. Muscles may feel sore or stiff and be sensitive to touch.[1] In some cases, statin-related myalgia can lead to poor adherence or discontinuation of the drug.[2]

The mechanism for statin-related myalgia is not fully understood, but vitamin D has been speculated to play a role.

Vitamin D deficiency itself is associated with symptoms of myalgia that resemble those caused by statins.[1,3] There has been speculation that statins themselves might affect vitamin D levels. Because low-density lipoprotein (LDL)-cholesterol is a vitamin D carrier and statins reduce LDL cholesterol, it has been proposed that statins could decrease vitamin D levels. On the other hand, both vitamin D and some statins are metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme. Owing to competitive inhibition at CYP3A4, it has been proposed that statins could increase levels of vitamin D.

Clinical trials and observational studies have produced mixed results in terms of the actual effect of statins on vitamin D levels. Overall, a meta-analysis of clinical trials found increased vitamin D levels in statin users.[4]
Several retrospective studies have shown that low vitamin D levels (measured as 25-hydroxyvitamin D) are associated with a higher risk for statin-induced myalgia. In a study by Shantha and colleagues, patients with vitamin D levels in the lowest quartile had a 1.21 times increased risk for statin-induced myalgia compared with those in the highest quartile. Levels of 15 ng/mL or lower positively predicted the development of myalgia in statin users.

In a cross-sectional study, statin-treated patients with vitamin D levels of less than 15 ng/mL had a 1.9 times increased odds of myalgia compared with non-statin users; however, statin users with higher vitamin D levels did not have an increased risk for myalgia compared with non-statin users. A retrospective chart review in veterans taking statins found that levels of vitamin D were approximately 10 ng/dL lower in those who experienced statin-induced myalgia compared with those who did not.

A meta-analysis of seven observational studies found that vitamin D levels were significantly lower in statin-treated patients who had symptoms of myalgia compared with those who were asymptomatic. The mean difference in vitamin D levels between the groups was approximately 9.4 ng/mL.

Not all studies have found an association between low vitamin D and myalgia, especially in studies evaluating patients with symptoms confirmed to be caused by statins. The discrepancies in findings may be because of the nonspecific nature of muscle symptoms. Some evidence shows that up to 50% of self-reported symptoms of muscle pain in statin users may not be because of statins specifically. Therefore, low vitamin D levels may contribute to muscle pain symptoms more generally, including in patients with statin-induced myalgia or nonspecific myalgia.

Assessing and treating low vitamin D levels may be worth considering before starting or restarting a statin in patients who develop muscle pain while taking a statin.

A retrospective chart review found that replenishing vitamin D before a statin rechallenge in previously intolerant patients increases statin tolerability and adherence.

In uncontrolled studies, some authors have used vitamin D2 (ergocalciferol) supplements (from 50,000 units to 100,000 units per week) in statin-treated patients with muscle symptoms and low vitamin D levels and reported resolution of myalgia in about 90% of patients. In these studies, low vitamin D levels were considered to be less than 32 ng/mL.
Introduction

Following an extensive review of the literature, the American Institute of Medicine (IOM) concluded that “myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) are serious, debilitating conditions that affect millions of people in the United States and around the world”; that it is a “medical - not a psychiatric or psychological - illness” without a “known cause or effective treatment” which “can cause significant impairment and disability” [1] rendering 25% of patients homebound or bedridden [2] yet “the term chronic fatigue syndrome can result in trivialization and stigmatization” of this “complex, multisystem, and often devastating disorder” [1]. Most doctors are unaware of the seriousness of ME or that it has been classified as a neurological disease by the World Health Organization (WHO) since 1969 [3]; therefore, patients often receive “hostility from their health care provider” and are “subjected to treatment strategies that exacerbate their symptoms” (i.e., CBT and GET) [1].

Abstract

The main findings reported in the PACE trial were that cognitive behavioral therapy (CBT) and graded exercise therapy (GET) were moderately effective treatments for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), and fear avoidance beliefs constituted the strongest mediator of both therapies. These findings have been challenged by patients and, more recently, a number of top scientists, after public health expert Tuller, highlighted methodological problems in the trial. As a doctor who has been bedridden with severe ME for a long period, I analyzed the PACE trial and its follow-up articles from the perspectives of a doctor and a patient. During the PACE trial the eligibility criteria, both subjective primary outcomes, and most of the recovery criteria were altered, creating an overlap of the eligibility and recovery criteria; consequently, 13% of patients were considered “recovered,” with respect to 1 or 2 primary outcomes, as soon as they entered the trial. In addition, 46% of patients
reported an increase in ME/CFS symptoms, 31% reported musculoskeletal and 19% reported neurological adverse events. Therefore the proportion negatively affected by CBT and GET would be between 46% and 96%, most likely estimated at 74%, as shown in a large survey recently conducted by the ME Association. Medication with such high rates of adverse events would be withdrawn with immediate effect. There was no difference in long-term outcomes between adaptive pacing therapy, CBT, GET and specialist medical care, and none of them were effective, invalidating the biopsychosocial model and use of CBT and GET for ME/CFS. The discovery that an increase in exercise tolerance did not lead to an increase in fitness means that an underlying physical problem prevented this; validates that ME/CFS is a physical disease and that none of the treatments studied addressed this issue.
Impaired calcium mobilization in natural killer cells from chronic fatigue syndrome/myalgic encephalomyelitis patients is associated with transient receptor potential melastatin 3 ion channels

Authors


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Summary

Transient receptor potential melastatin subfamily 3 (TRPM3) ion channels play a role in calcium (Ca\(^{2+}\)) cell signalling. Reduced TRPM3 protein expression has been identified in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) patients. However, the significance of TRPM3 and association with intracellular Ca\(^{2+}\) mobilization has yet to be determined. Fifteen CFS/ME patients (mean age 48.82 ± 9.83 years) and 25 healthy controls (mean age 39.2 ± 12.12 years) were examined. Isolated natural killer (NK) cells were labelled with fluorescent antibodies to determine TRPM3, CD107a and CD69 receptors on CD56\(^{\text{dim}}\)CD16\(^{+}\) NK cells and CD56\(^{\text{bright}}\)CD16\(^{\text{dim}}\) NK cells. Ca\(^{2+}\) flux and NK cytotoxicity activity was measured under various stimulants, including pregnenolone sulphate (PregS), thapsigargin (TG), 2-aminoethoxydiphenyl borate (2APB) and ionomycin. Unstimulated CD56\(^{\text{dim}}\)CD16\(^{+}\) NK cells showed significantly reduced TRPM3 receptors in CFS/ME compared with healthy controls (HC). Ca\(^{2+}\) flux showed no significant difference between groups. Moreover, PregS-stimulated CD56\(^{\text{dim}}\)CD16\(^{+}\) NK cells showed a significant increase in Ca\(^{2+}\) flux in CFS/ME patients compared with HC. By comparison, unstimulated CD56\(^{\text{dim}}\)CD16\(^{+}\) NK cells showed no significant difference in both Ca\(^{2+}\) flux and NK cytotoxicity activity was measured under various stimulants, including pregnenolone sulphate (PregS), thapsigargin (TG), 2-aminoethoxydiphenyl borate (2APB) and ionomycin. Unstimulated CD56\(^{\text{dim}}\)CD16\(^{+}\) NK cells showed significantly reduced TRPM3 receptors in CFS/ME compared with healthy controls (HC). Ca\(^{2+}\) flux showed no significant difference between groups. Moreover, PregS-stimulated CD56\(^{\text{dim}}\)CD16\(^{+}\) NK cells showed a significant increase in Ca\(^{2+}\) flux in CFS/ME patients compared with HC. Furthermore, TG-stimulated CD56\(^{\text{dim}}\)CD16\(^{+}\) NK cells increased K562 cell lysis prior to PregS stimulation in CFS/ME patients compared with HC. Differential expression of TRPM3 and Ca\(^{2+}\) flux between NK cell subtypes may provide evidence for their role in the pathomechanism involving NK cell cytotoxicity activity in CFS/ME.